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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,967	12/02/2003	Marcus Ballinger	2004345-0021 (SU-2600 US)	4388

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/726,967	BALLINGER, MARCUS	
	Examiner	Art Unit	
	Sheridan L. Swope	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20* is/are rejected.

7)☒ Claim(s) *18-20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0404*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Applicant's election of Invention II, Claims 18-20, as well as the autoproteolysis site of SEQ ID NO: 57, the protease domain of SEQ ID NO: 52, and the prodomain of residues 22-41 of SEQ ID NO: 1, in their response of July 5, 2005, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-20 are pending. Claims 1-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 18-20 are hereby examined.

Specification-Objections

Abstract

The Abstract is objected to for being two paragraphs. Correction is required. See MPEP § 608.01(b).

Claims-Objections

Claims 18-20 are objected to for being dependent from a non-elected claim.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

In this regard, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding the polypeptides of SEQ ID NO: 81 and 84, does not reasonably provide enablement for any polynucleotide encoding any polypeptide comprising any prodomain derived from SEQ ID NO: 3, any protease cleavage site, and any protease domain having BACE activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 18 is so broad as to encompass any polynucleotide sequence that encodes any protein comprising any prodomain derived from SEQ ID NO: 3, any protease cleavage site, and any protease domain having BACE activity. Claim 19 is so broad as to encompass any vector that can be used for expressing said any protein. Claim 20 is so broad as to encompass any host

cell expressing said any protein. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired protease cleavage site and BACE activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to polynucleotides encoding the proteins of SEQ ID NO: 81 and 84.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Wishart et al, 1995; Witkowski et al, 1999). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 18-20, which encompasses all polynucleotide sequences that encode a protein having any prodomain derived from SEQ ID NO: 3, any protease cleavage site, and any protease domain having BACE activity, any vector that can be used for expressing said any protein, and any host cell expressing said any protein,

respectively. The specification does not support the broad scope of Claims 18-20 because the specification does not establish: (A) all sequences for the encompassed protease cleavage sites; (B) any protein having BACE protease activity wherein said activity is due to a domain consisting of the sequence of SEQ ID NO: 52; (C) regions of the protein structure which may be modified without effecting any cleavage site or the BACE activity; (D) the general tolerance of any cleavage site or BACE activity to modification and extent of such tolerance; (E) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of polynucleotides encoding any polypeptide comprising any prodomain derived from SEQ ID NO: 3, any protease cleavage site, and any protease domain having BACE activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 18 is directed to a genus of nucleic acid molecules encoding any polypeptide comprising any prodomain derived from SEQ ID NO: 3, any protease cleavage site, and any protease domain having BACE activity. The specification teaches the structure of only two representative species of such nucleic acid molecules. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a polypeptide comprising any prodomain derived from SEQ ID NO: 3, any protease cleavage site, and any protease domain having BACE activity. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 18-20 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Gurney et al, 2002, which has a filing date of October 13, 1999 (IDS). Gurney et al teach a polynucleotide (SEQ ID NO: 3 therein) encoding a BACE protein (SEQ ID NO: 4 therein), wherein residues 22-37 of said protein are identical to the prodomain of SEQ ID NO: 3 herein, residues 22-41 of said protein are identical to the protease domain of residues 22-41 of SEQ ID NO: 1 herein, and residues 74-101 of said protein are identical to the putative protease domain of SEQ ID NO: 52 herein. Gurney et al also teach the polynucleotide of SEQ ID NO: 3 further comprising a sequence encoding the engineered protease cleavage site set forth by LEVLFQGP (SEQ ID NO: 62), as well as vectors and host cells comprising said polynucleotide (col 18, parg 1). Therefore, Claims 18-20 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Gurney et al, 2002.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gruney et al, 2002 in view of Turner et al, 2001 (IDS) and further in view of Ermolieff et al, 2000. The teachings of Gurney et al are described above. Gurney et al do not teach a polynucleotide encoding a polypeptide comprising the motif EINLETD, the autoproteolysis cleavage site elected by Applicants. Using a library of peptides consisting of eight residues, Turner et al teach a series of protease cleave sites preferred by BACE. Figure 1 discloses that a preferred site for

cleavage by BACE comprises the motif EINLE, with cleavage between Leu and Glu. Figure 1 further discloses that, Thr and Asp residues in positions six and seven, although not optimal, support cleavage by BACE and that the residue at position eight is not critical. For the following reasons it would have been obvious to a person of ordinary skill in the art to prepare a polynucleotide encoding the protein of Gurney et al (SEQ ID NO: 4 therein), wherein said protein further comprises the protease cleavage site EINLETD. It is known in the art that BACE is synthesized as a preproprotein, which is cleaved between residues Arg^{32}/Glu^{33} of the motif RLPRETD (Ermolieff et al, pg 12450, parg 2, – pg 12450, parg 1). Ermolieff et al teach that cleavage of BACE at Gly^{27}/Leu^{28} or Arg^{44}/Gly^{45} releases BACE from auto-inhibition, thus activating the enzyme (Table 1 & Fig 8). Since cleavage of BACE at Gly^{27}/Leu^{28} or Arg^{44}/Gly^{45} releases BACE from auto-inhibition, Ermolieff et al teaches that cleavage at Arg^{32}/Glu^{33} also activates the enzyme (pg 12455, parg 2, - pg 12456, parg 1). Thus, one would be motivated to engineer a protease cleavage site at Leu^{32}/Glu^{33} within the motif EINLETD for the following reasons. As taught by Turner et al, EINLETD is a preferred site for cleavage by BACE and inserting said site supports autoproteolysis and, thus, efficient processing of BACE to the active, mature form having the N-terminal ETD- sequence. The expectation of success is high as, using recombinant techniques, which are well known in the art, the RLPRETD site within BACE, which is cleaved by an exogenous protein, can be easily converted to the autoproteolysis EINLETD cleavage site. Therefore, Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gruney et al, 2002 in view of Turner et al, 2001 and further in view of Ermolieff et al, 2000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.

Art Unit 1656